NEW YORK HEART ASSOCIATION

ABSTRACTS OF PAPERS SUBMITTED FOR PRESENTATION AT THE SCIENTIFIC SESSION ON RESEARCH HELD AT THE NEW YORK ACADEMY OF MEDICINE, APRIL 25, 1968

On the Nature of the Tachycardia that Follows Vagal Stimulation

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Termination of vagal stimulation is followed by a transient sinus tachycardia. This "postvagal" tachycardia could result from: 1) a reflex release of catecholamines due to the fall in blood pressure during vagal stimulation; 2) reflex vagal withdrawal also due to hypotension; and 3) direct release of catecholamines by the vagus. In anesthetized dogs the peripheral end of the vagus was stimulated. The postvagal tachycardia occurred whether the blood pressure during vagal stimulation was maintained or was allowed to fall. Also, the postvagal tachycardia persisted after bilateral vagotomy. To avoid stimulation of sympathetic fibers which might be present in the vagus, the vagus was stimulated reflexly by increasing the carotid sinus pressure. This procedure was also followed by tachycardia. Bilateral vagotomy abolished this response. Tetraethylammonium applied locally on the sinus node blocked the vagus-induced tachycardia. Postvagal tachycardia was also abolished by reserpinization and restored after norepinephrine administration in reserpinized dogs. It is suggested that postvagal tachycardia results from the excitation of cholinergic parasympathetic fibers, which leads to liberation of catecholamines possibly from chromaffin cells. *(Supported by a grant from the American Heart Association.)*

Cerebrovascular Spasm: Its Production and Modification in the Laboratory Animal

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Monkeys anesthetized with pentothal have undergone transclival exposure of the basilar and vertebral arteries and the ventral aspect of the brainstem.

After the arrachnoid has been opened, local arterial spasm has been consistently produced by the application of fresh arterial blood-soaked pledgets to the arterial wall

for one to two minutes. Other substances that produce this local arterial response have not been found. Photographic documentation through the operating microscope has revealed that a high degree of spasm is produced in this manner.

Significant spasm of the basilar and vertebral arteries is generally accompanied by a fall in systemic blood pressure with a subsequent return to normal levels with return of the arterial caliber to a more normal size.

Preliminary investigation of factors that modify this spasm have been undertaken. Controlled hypothermia does not appear to raise the threshold for the induction of spasm, nor to reduce its severity. On the contrary spasm may be abnormally prolonged during hypothermia. The character of the changes induced under hypotension and a combination of hypotension and hypothermia have also been documented.

While the mediating factors involved in the production of spasm remain obscure, some preliminary information has been obtained about the neural mechanisms involved by the use of the dry-fluorescent staining technique of catecholamine-containing fibers. Our observations would suggest that these fibers may play a part in the production of spasm, because of a change in the catecholamine content of the mural nerves of those arteries in spasm, when compared to normal arteries. *(Supported by Neurosurgical Research Fund.)*

Factors Involved in Maintenance of Cardiac Catecholamine Content

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Cardiac catecholamine concentrations remain normally at a steady level, even in the face of massive release as a result of vigorous sympathetic activity. Increased sympathetic activity results in enhancement of the rate of synthesis of norepinephrine to compensate for the transmitter losses induced by impulse discharge.

There is, however, a definite limit to the rise of adrenergic transmitter synthesis during increased sympathetic nervous activity, since endogenous amine levels in the heart decreased when animals pretreated with drugs (imipramine, phenoxybenzamine, cocaine, etc.) known to inhibit the uptake of norepinephrine into the nerve terminal were subjected to high-impulse activity associated with cold. Parathyroidectomy was found to have a similar effect. Thus it appears that reincorporation of released norepinephrine also contributed greatly to the maintenance of transmitter stores during high impulse activity. In fact, the reuptake was increased during such activity.

It is concluded that under normal conditions the reuptake mechanism does not play a significant role in the maintenance of normal cardiac catecholamine levels and that such levels are maintained by synthesis alone. However, when the heart is subjected to high-impulse nerve activity, synthesis is not sufficiently accelerated to compensate for the impulse-induced massive release and may require the support of an additional mechanism, such as the partial reincorporation of released transmitter. *(Supported by a grant from the Tobacco Research Council, U.S.A., and U.S.P.H.S. Grant 00890-17.)*

The Effects of Angiocardiography on Fluid and Electrolyte Balance and Acid-Base Equilibrium

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The effects of intravenous 75 per cent Hypaque on fluid and electrolyte balance and acid-base equilibrium in infants and children with congenital heart disease undergoing diagnostic cardiac catheterization was determined in 29 patients aged 1 month to 18 years. Thirteen patients had cyanotic congenital heart disease. Fifty studies were performed. One cc./kg. body weight of the contrast material was delivered within one second for each selective angiocardiogram. Control values for serum sodium, potassium, BUN, bicarbonate, osmolality, *p*H, hemoglobin, and hematocrit were obtained immediately before the first angiocardiogram and at 5, 15, 30, and 180 minutes thereafter. A fall in BUN, serum potassium, *p*H, bicarbonate, hematocrit, and hemoglobin occurred within five minutes after the injection of the contrast material. These values returned to near normal levels by 15 to 30 minutes. There was a rise in serum osmolality at 5 minutes with return to normal by 30 minutes. No fixed pattern was noted in the sodium and chloride values. In patients who had had repeated angiocardiograms prior to the return of these parameters to normal, the changes were more marked and progressive. Analysis of the data obtained in this study showed an immediate and marked dilutional and acidotic effect of intravenous Hypaque, with return to normal levels by 15 to 30 minutes. Repeat angiocardiography at shorter intervals than this should therefore be avoided, especially in infants in cardiac failure, in infants receiving digitalis, and in cyanotic patients, to allow for recovery from these acute biochemical effects and to prevent the development of acidosis and hypokalemia.

Vasomotor Nature of Discharge in a Preganglionic Sympathetic Nerve

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The efferent discharges of the splanchnic and phrenic nerves were recorded in decerebrate or urethane-anesthetized cats paralyzed with gallamine or decamethonium chloride and artificially ventilated after pneumothorax and vagotomy. The efferent splanchnic nerve activity (monophasically recorded with a bandwidth of 0.2-1000 c./sec.) consisted of groups of waves (usually at 10/sec.) which also oscillated in phase with both the cardiac and central respiratory cycles. The discharge of this nerve was studied as a sample of sympathetic outflow and was shown to be a useful indicator of vasomotor activity by the observations in a variety of conditions of close relations between the level of discharge and of arterial blood pressure. It was found that increases or decreases of splanchnic activity were followed by increases or decreases, respectively, of blood pressure. This relation held true for spontaneously occurring changes, changes induced by cardiovascular manipulations, and changes induced by electrical

stimulation of brain stem points. Following conditions which produced a fall in arterial pressure, e.g., hemorrhage and common carotid artery occlusion, and therefore a decrease in baroreceptor discharge, there was a compensatory increase of splanchnic discharge and of blood pressure. The converse effects were observed following an induced blood pressure rise, e.g., by aortic occlusion.

Both high- and low-frequency electrical stimulation were employed at brain stem points and observations were made of their effects on both blood pressure and splanchnic discharge. The existence of special pressor and depressor regions in the medulla oblongata was supported by the observations that the loci which gave the shortest latency splanchnic responses to single shocks also gave the greatest changes of blood pressure and splanchnic discharge to high-frequency stimulation. *(Supported by U.S.P.H.S. grants NIH-2TI-NB5304, NIH-NB-03970, and NIH-NB-06590.)*

Myocardial Actomyosin and Total Protein in Isoproterenol-Induced Hypertrophy

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These studies concerned an evaluation of the actomyosin and total protein content of the heart in isoproterenol-induced hypertrophy in rats.

Paired groups of animals of the same initial average body weight (range: 235 to 275 gm.) were injected daily, subcutaneously, with either isoproterenol, 5.25 mg./kg. or the diluent for 1, 7, and 14 days.

Cardiac hypertrophy was determined by direct comparison of heart weights of the drug-treated groups with those of the control groups for each treatment period. Heart weight:body weight ratios were purposely not used to evaluate hypertrophy since we observed that the isoproterenol-injected animals gained an average of 50% less weight than the placebo-injected animals. Therefore heart weight:final body weight ratios would result in a serious bias for hypertrophy measurements. Dry heart weights in the isoproterenol groups showed increases of 16, 29, and 47% for 1, 7, and 14 days of treatment respectively.

Extraction of actomyosin and determinations of protein were carried out as described previously (Inchiosa. *Amer. J. Physiol. 206*:541, 1964). Our preliminary data indicate no marked changes in cardiac actomyosin or total protein content as a percentage of dry tissue weight. However total ventricular actomyosin and total protein were markedly increased in proportion to the hypertrophy. Total ventricular actomyosin was increased 13, 27, and 38% for 1, 7, and 14 days respectively. Total ventricular protein was increased 17, 21, and 46% respectively for the same treatment periods.

Since it has been shown that isoproterenol (5.25 mg./kg.) causes myocardial necrosis (Lehr, Krukowski, and Colon. *J.A.M.A. 197*:105, 1966), we examined the hypertrophied hearts for the possible presence of breakdown products of proteins. In three drug-treated animals no evidence was found for the presence of tricholoroacetic acid (TCA)-soluble fragments of protein. The three treated animals and two placebo-injected animals all showed identical protein contents of the tissue homogenates before and after TCA extraction. *(Supported by a grant from the New York Heart Association and by U.S.P.H.S. Grant HE-00890-17.)*

Separated Spike and Plateau Action Potentials and Their Roles in the Excitation-Contraction Coupling of the Frog Ventricle

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Effects of tetrodotoxin (TTX) and Mn^{++} on the membrane potentials and contractility of the frog ventricle were studied with microelectrode and mass polarization methods.

Mn^{++} (10 to 20 m*M*) produced first a gradual diminution and then sudden disappearance of the plateau potential and contraction; it left only a sharp spike potential behind. Strengthening of mass depolarizing current, however, elicited an all-or-nothing type of appearance of the plateau and contraction, while weakening of the current eliminated them. Thus, two thresholds, one for spike generation and the other for plateau potential were observed markedly separated. After washing, the difference between two thresholds diminished, and finally separation of the spike from the plateau became impossible. Under the conditions of these experiments twitch contractions occurred only with the appearance of the plateau, never with the spike alone.

TTX (10^{-7} gm./ml.) produced a marked decrease in rate of rise and height of the spike potential as well as a conspicuous elevation of the threshold. The diminution of spike height below a certain level, however, abolished the appearance of plateau in the presence of Mn^{++}. Strong mass depolarizing current could produce a slow plateau-like potential in this condition, but this potential appeared rather graded in nature. After washing, the spike recovered first and then the plateau and contraction followed.

In normal preparations, strong and long continued depolarizing current elicited first phasic and second tonic contractions corresponding to an augmented action potential and a subsequent sustained depolarization respectively.* TTX and complete lack of Na^{+} were found to eliminate the phasic contraction but not the tonic one, while Mn^{++} and deficiency of Ca^{++} diminished both of them.

These observations strongly suggest that the spike potential, due to the influx of Na^{+}, triggers the plateau potential, which relates somehow with the influx or release of Ca^{++}; the consequent increase of free intracellular Ca^{++} elicits the contraction.

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*Goto, M. and Brooks, C. McC. (1968) Federation Meeting.

A Method for Determination of Pulmonary Artery Blood Volume Using Macroaggregated I^{131} Human Serum Albumin

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Determination of pulmonary artery blood volume (PAV) may be useful in differentiating active vasomotor changes from passive mechanical changes in the pulmonary arterial bed. Active vasoconstriction should be accompanied by a decrease in blood volume and passive changes, by an increase in blood volume.

A method for determination of PAV has been developed that uses macroaggregated

I^{131} albumin (MAA). When injected into the venous circulation MAA is trapped in the precapillary vessels of the lungs. An estimate of the pulmonary arterial circulation time was obtained from the injection of MAA into the right atrium by using two counters: one colimated over the precordium and one over the periphery of the lung. PAV was calculated by multiplying pulmonary arterial transit time (PATT) by blood flow.

After an initial delay, activity in the lung rose in stepwise fashion. The increase in activity was abrupt; it lasted 0.04 to 0.08 sec. and was followed by a plateau during the remainder of the heart cycle. The rate of wash-in to the lungs was substantially the same as the rate of wash-out from the right ventricle. It is apparent that the precapillary pulmonary vasculature is essentially a transit section, producing little dispersion of the indicator. Therefore the time from the opening of the pulmonic valve to first appearance of the tracer in the periphery of the lung was taken as the PATT.

In eight dogs (15 to 24 kg.) PATT was 0.36-1.48 sec. (mean 0.86.). The PAV was 14 to 78 ml. (mean 52 ml.). PATT varied inversely as the pulmonary blood flow ($r = 0.69$) and directly as the circulation time through the entire pulmonary vascular bed ($r = 0.78$). PAV constituted 17 to 30 per cent of the total pulmonary blood volume (mean 21 per cent).

In one man, PAV was 160 ml. and constituted 20 per cent of the total pulmonary blood volume.

Role of Calcium in Cardiac Pacemaker Cell Action

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It was reported by Seifen *et al.* (*Nature 202*:1223, 1964) that a change in calcium concentration in the perfusate not only altered the threshold but also the speed of diastolic depolarization of an SA node pacemaker cell. High calcium accelerated the diastolic depolarization. Yamagishi *et al.* (*Proc. Jap. Acad. 42*:1194, 1966) reported that tetrodotoxin in dose sufficient to abolish the action potential of an atrial cell had little effect on the action potential of an SA node pacemaker cell. A further study of the relation between Na^+, Ca^{++}, and pacemaker cell activities in isolated SA nodes of cat and rabbit was conducted in various conditions by use of microelectrode recording technique. The results confirmed the finding reported by Seifen *et al.* and Yamagishi *et al.* and revealed, in addition, the following phenomena:

1) High Ca^{++} concentration in the perfusate potentiated the stretch-induced acceleration of the firing rate of a pacemaker cell. Low Ca^{++} had the opposite effect. The same response was obtained from reserpine-pretreated preparations.

2) Manganese suppressed both the diastolic depolarization and the action potential of a true spacemaker cell to various degrees according to the concentration used. This suppressive effect of manganese could be partially counteracted by raising the Ca^{++} concentration in the perfusate.

3) Latent pacemaker and atrial cells could still be excited when treated with manganese in a concentration sufficient to suppress the action potential of a true pacemaker cell. The action potentials disappeared after a subsequent treatment with tetrodotoxin.

4) In a pacemaker cell which showed only oscillation of membrane potential but no propagating action potentials, high Ca^{++} potentiated and low Ca^{++} diminished the late acceleratory effect of overdrive on the pacemaker activity.

It is postulated that Ca^{++} flux plays an important role in the development of diastolic depolarization and the formation of action potentials in an SA node pacemaker cell. *(Supported by a grant from the New York Heart Association.)*

Vascular Effects of Potassium Ion

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To investigate the vasoactive properties of potassium the cation was infused via a fine catheter positioned in the isolated canine femoral artery, and the flows were determined by means of a calibrated dual channel square wave electromagnetic flowmeter. Control blood flows were measured in the contralateral femoral artery while systemic pressures were obtained from the cannulated carotid artery. All parameters were inscribed by a direct writing physiologic recorder. Intra-arterial infusion of potassium resulted in a dose-related characteristic biphasic response. Below 8 mEq./l. vasodilatation occurred. Concentrations greater than 8 mEq./l. caused vasoconstriction of the ipsilateral and vasodilatation of the contralateral femoral arteries, a rise in systemic pressure and an increase in flow of the mesenteric, renal, vertebral, and brachial arteries. Upon cessation of potassium instillations the infused limb routinely exhibited an afterdilatation. Mediation of these vascular changes either by humoral agents, neural pathways, or direct kalemic action on the vessel wall was studied. Classical adrenergic blockade with alpha receptor (Regitine) and Beta receptor (propranalol) inhibitors, antihistamines, and serotin antagonists failed to suppress, and ganglionic blockade with arfonad failed to inhibit the cationic vascular effects. Simultaneous magnesium ion infusion with high concentrations of potassium ion prevented kalemic induced vasoconstriction. Our findings suggest that potassium vasoactivity is achieved through a direct action upon the blood vessel wall. On the basis of a distinct similarity between kalemic and adrenergic humoral vasoactivity a concept is advanced that involves potassium in a final common pathway to the contractile process in vascular smooth muscle. In the chain reaction of neurovascular transmission-activation and in terms of conventional membrane theory it appears that potassium acts at a site peripheral to the sympathetic agents. *(Supported by U.S.P.H.S. Grant SO1-FR-00502.)*

Methods for Increasing the Efficiency of a New Disposable Membrane Oxygenator

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Experience with short (5 cm.), rigidly supported parallel blood flow path membrane oxygenators has confirmed the effectiveness of several methods for increasing gas exchange. These methods may be applied without equivalent increases in blood damage.

Due to the extremely short, wide, fluid

flow paths, blood may be recirculated through the devices at rates several times the rate of flow to and from the patient without excessive pressure drops. Boundary layer effects are thus reduced. Secondary mixing in the laminar blood flow, which occurs as a result of the sine wave configuration of blood flowing between these Bluemele cone-supported membranes is increased in recirculation.

Intermittent ultrathin filming of the blood by occluding the dialysate or O_2 outflow further augments efficiency besides allowing venoarterial pumping with the oxygenators themselves. The effect of high-frequency vibration transmitted through the rigid support plates is also being assessed.

Oxygen transfers in excess of 70 cc./m.^{2} of membrane per minute *in vivo* preparations have been achieved. *In vitro* studies of hemolysis, platelet loss, and protein denaturation have shown little or no increase accompanying use of the methods outlined above. This is because velocities and shear rates actually remain quite small in these parallel flow path devices. *(Supported by U.S.P.H.S. grants NIH-PH-43-67-1446, and NIH-PH-43-67-1379.)*

Long-Term Function of Prosthetic Valves Inserted into the Tricuspid Annulus of the Calf as Determined by Their Interface Charge

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Studies in our laboratory have defined certain electrochemical factors in thrombosis: 1) the normal blood vessel has a uniform negatively charged surface, 2) metals high in the electromotive series such as aluminum, which have a negative surface in blood, tend not to induce thrombosis, 3) metals low in the electromotive series, such as copper, which have a positive surface in blood, thrombose invariably. It has become apparent, however, that surface contaminants such as metallic impurities, oxide formation, silicates, and organic contaminants may disrupt the uniformity of a prosthetic surface and induce thrombosis in spite of a net negative surface charge.

Identical castings of a Sawyer modification of the Starr-Edwards ball-valve prosthesis were made of commercial aluminum, stellite 21, N-155, and commercial copper. A control series was implanted with the "dirty" factory surface. In other series the surfaces were oxidized with concentrated nitric acid and/or reduced with concentrated hydrochloric acid. The surface potential of each valve was measured in contact with the blood of the animal into which it was to be inserted.

The results show that prostheses of metals or of alloys containing elements, either as impurities or as constituents, widely separated in the electromotive series, or which tend to oxide formation, or which have on their surface silicate, organic, or other contaminants, have a mixed interfacial potential in blood. The surfaces are not uniform and may induce thrombosis in spite of a net negative surface charge. *(Supported by U.S.P.H.S. grants HE 07371 and HE 10795 and by U.S.P.H.S. Contract PH 43-68-75.)*

Renal Interstitial Pressure During Exaggerated Natriuresis in Essential Hypertension

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The mechanism responsible for decreased tubular reabsorption of sodium during exaggerated natriuresis in hypertensive man is unknown. Studies in animals have related increased renal interstitial pressure to reduced net sodium transport in the proximal tubule. In the present study we have found that calculated glomerular pressure and renal interstitial pressure as measured by wedged renal vein pressure (WRVP) are increased during exaggerated natriuresis in man. In five patients with early essential hypertension, retrograde catheterization of the renal vein was performed and a subselective catheter was "wedged" in a small venous branch. Control GFR and renal plasma flow averaged 113 ml./min. and 413 ml./min. respectively; WRVP averaged 26 mm. Hg (range 23 to 27 mm. Hg). Following rapid intravenous administration (17.5 ml./min.) of 2.5% saline, average sodium excretion increased from 305 μEq./min. to 1680 μEq./min. GFR increased in four patients and was unchanged in one. Renal plasma flow increased in four. WRVP increased in each patient, averaging 53 mm. Hg (range 34 to 66 mm. Hg) at the peak of natriuresis. Mean arterial pressure increased from 125 to 136 mm. Hg while afferent arteriolar resistance decreased from 4911 to 3126 dyne sec. cm.$^{-5}$, and efferent resistance was unchanged. Calculated glomerular pressure increased from a mean of 74 mm. Hg to 96 mm. Hg. We have previously shown during solute diuresis with mannitol that renal interstitial pressure is increased and GFR is decreased, presumably as a consequence of increased tubular hydrostatic pressure. The hemodynamic response to saline differs in that a marked increase in glomerular pressure occurred and GFR did not fall, indicating that the increase in interstitial pressure during saline is due, at least in part, to a decrease in resistance between the systemic circulation and the renal interstitium. The demonstration that the renal hemodynamic response to saline is characterized by increased glomerular and renal interstitial pressures provides a possible explanation for the decreased reabsorption of sodium during exaggerated natriuresis in hypertensive man. *(Supported by U.S.P.H.S. Grant NIH-HE-03272.)*

Renal Vein and Peripheral Vein Renin Assay in Patients with Chronic Renal Failure on Medical and Hemodialysis Treatment

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The significance of renin secretion in the pathogenesis of hypertension associated with renal failure is not defined. In this study we have measured renin activity in periph-

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eral vein (PVR) and renal veins (RVR) of 9 patients with medically treated renal failure and 11 patients with renal failure who were receiving hemodialysis. Comparison is made with studies in 10 patients with essential hypertension and 3 patients with renovascular hypertension.

In essential hypertension, all measurements were normal: PVR $<$ 900 nanograms per 100 ml. (ng%); RVR $<$ 1200 ng%. In 3 patients with renovascular hypertension, RVR $>$ 5000 ng% from the ischemic kidney.

PVR was normal in 9 hypertensive patients with medically treated renal failure. In 2 patients RVR from one kidney was between 1200 and 2000 ng%. RVR was normal in the remaining 7 patients. Of 11 patients receiving hemodialysis treatment, PVR was greater than 900 ng% in 4 patients. In studies of 2 patients with increased PVR, RVR was greater than 1900 ng% from both kidneys.

These values suggest a somewhat greater frequency of increased renin secretion in patients receiving hemodialysis. The fact that renin secretion may vary widely in patients receiving hemodialysis is an indication for making this measurement prior to bilateral nephrectomy. Without prospective evaluation, the variable effect of bilateral nephrectomy upon the hypertension is difficult to interpret, and hypertensive mechanisms unrelated to excess renin release may not be defined. *(Supported by Bernard Ruderman.)*

Hemodynamic Problems in Designing an Artificial Right Ventricle

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These studies deal with hemodynamic problems related to a right ventricular substitute. The following aspects important in the design of the ventricle proper as well as its pumping system were evaluated: 1) a comparison of pneumatic and hydraulic actuation methods that used a mock circulation; 2) the most suitable type of valve mechanism for the inflow tract; and 3) configuration of the outflow tract.

Water was used as the circulating fluid in all experiments. The artificial heart used consists of a rigid outer chamber of lucite divided in two compartments by a compressible Silastic membrane. The results indicate that with pneumatic actuation, output increases proportional to the pulse rate up to a level of 100 per minute but decreases when the pulse rate exceeds 100 per minute or the output pressure load increases to above 77 mm. Hg. Hydraulic pumping does not decrease under these conditions. Evaluation of a caged ball valve at the inflow tract reveals high-pressure gradients across the valve at a high flow rate, which indicates that this type of valve is not suitable. An oblique discoid valve with minimal pressure gradients was developed for this purpose and will be described. Outflow tract experiments indicate that a short-large diameter outflow tube produced maximum flow with minimal pressure elevations. The data suggest that: 1) pneumatic actuation is not suitable for a left heart substitute but could be applied to a right heart substitute; 2) an oblique discoid valve is preferable to a caged ball valve at the inflow tract; and 3) the outflow tract of a right heart substitute should be short and of large diameter. *(Supported by The Clift Cardiovascular Fund.)*

Effects of Bile Diversion on Cholesterol Biosynthesis in Dogs

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Long-term balance studies have been performed in dogs before and after diversion of bile from the intestinal tract in an attempt to study the effects of interruption of the enterohepatic circulation of cholesterol and bile acids upon biosynthesis of cholesterol.

Five dogs were studied in the intact state, and two of these were then subjected to *complete* diversion of bile into the urinary stream through a cholecystonephrostomy. All animals were fed a semisynthetic cholesterol-free diet in pellet form for 16 months in amounts sufficient to maintain constant body weight. Quantitative analysis of biliary and fecal neutral steroids and bile acids was carried out by chromatographic and isotopic methods developed in this laboratory.

In the metabolic steady state the daily excretion of neutral and acidic steroids in urine and feces represents the amount of cholesterol synthesized daily. Measurements of these two classes of steroids showed that, following diversion of bile, total daily synthesis of cholesterol increased approximately sevenfold. Bile acids in "urine" constituted the largest fraction excreted, but there was also a striking increase in fecal neutral steroids, despite complete interruption of the enterohepatic circulation.

Three precursors of cholesterol were found unexpectedly in the "urine" of bile-diverted dogs: by thin-layer and gas-liquid chromatographic criteria, these were tentatively identified as dihydrolanosterol and lanosterol (C_{30}) and methostenol (C_{28}). After intravenous injection of 2-^{3}H-LD-mevalonic acid, specific activity time curves of the ($C_{30} + C_{28}$) and (C_{27}) sterols were compared; these curves showed the expected precursor-product relation. The presence of these cholesterol precursors in bile has not previously been reported.

Summary. In bile-diverted dogs cholesterol synthesis was enhanced sevenfold, and there was evidence of C_{30} and C_{28} precursors in the bile when cholesterol biosynthesis was thus maximized. Despite complete bile diversion considerable amounts of cholesterol and coprostanol continued to be excreted in the stool. This laboratory model should prove useful in studies of the effects of drugs on cholesterol biosynthesis. *(Supported in part by U.S.P.H.S. GM-01-706-01.)*

Comparison of Influence of Alpha-Methyl-Tyrosine and Dibenzyline on Circulatory Effects of Ganglionic Stimulation in Anesthetized Dogs

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Alpha-methyl-tyrosine (AMT) is an inhibitor of the enzyme tyrosine hydroxylase which regulates the rate of synthesis of norepinephrine (NE); this results in diminished vasopressor responses to sympathetic stimulation. Dibenzyline's action as an alpha-blocking agent has been widely discussed.

Experiments were designed to quantitate and compare the effects of AMT and dibenzyline (DBZ) in a catecholamine/peripheral blood flow model in the intact anesthetized dog, and to observe the comparative circulatory effects of electric stimulation of sympathetic ganglia. Thirty-eight mongrel dogs were anesthetized with morphine and chloralose, splenectomy performed, and lumbar sympathetic chain exposed for electric stimulation with 15 volt square waves of 2 msec. duration, 30 times per second. Femoral artery blood flow (ml./min., electromagnetic flow probe), perfusion (ml./100 gm./min.) of hind limb (Whitney plethysmograph), and determination of norepinephrine (NE) in arterial wall (NE_t) (μg./gm.) and in plasma (NE_p), and epinephrine in plasma (E_p) (μg./l.) were determined. AMT (100 mg./kg.) and DBZ (5 mgm./kg.) were infused into respective groups, and observations were made.

Alpha-methyl-tyrosine did not cause changes in heart rate or blood pressure, while DBZ increased the heart rate 100 beats/min. above control and lowered mean systemic arterial BP 25%. Concentrations of norepinephrine in plasma rose significantly in response to electric stimulation of lumbar sympathetic ganglia in control animals and in those treated with dibenzyline, but not in animals given AMT. Stimulation caused no reduction in femoral artery flow in dogs treated with DBZ, in contrast to decreases of 54% and 20% in untreated and AMT-treated dogs. Stimulation reduced perfusion 80% in untreated dogs but only 20% after treatment with either drug.

It is concluded that AMT is an effective drug to combat vasoconstrictive consequences of sympathetic stimulation. It has fewer undesirable side effects than DBZ. The different mechanisms and sites of action of each drug have been demonstrated.

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Alpha-2 Hyperglobulinemia as a Humoral Indicator of the Homograft Reaction

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Serial serum protein studies were performed on 26 patients following renal transplantation. This study attempted to correlate alterations in the serum proteins with the onset and course of a rejection episode. Following admission to the transplant service, all patients underwent a battery of blood tests prior to their transplantation, and such tests were continued periodically throughout their hospital course and thereafter via our transplant clinic. These tests included the following: total protein—A/G ratio; serum and urine electrophoresis; serum and urine protein ultracentrifugation; serum and urine immunoelectrophoresis; selective qualitative glycoprotein and lipoprotein staining and starch gel electrophoresis. The diagnosis of graft rejection was based on a variety of clinical and laboratory tests including: fever, oliguria, azotemia, changes in creatinine and urea clearance, proteinuria, etc.

Among the 26 patients used in this study, 17 experienced a total of 28 rejection episodes over a 4 year period. The most consistent serum alteration observed during a rejection episode was the appearance of an elevated alpha-2 glycoprotein. The presence of this protein(s) usually did not appear in the serum until there was overt evidence of a rejection episode. When the graft rejection was aborted (usually by increased doses of prednisolone), the elevated alpha-2 glycoprotein returned to a prerejection level (17 cases). If remission was not effected or the process became chronic in course, this fraction remained elevated as long as the graft remained in-situ (8 cases).

This protein was not elevated during the course of several intercurrent illnesses simulating graft rejection: recurrent GNP (2 cases); septicemia or severe peritonitis (5 cases); hepatitis; acute hypercalmemia (2 cases). In 1 patient, this protein was found elevated in the absence of graft rejection.

The identity of this protein has not been ascertained. To date, qualitative tests have excluded haptoglobin, ceruloplasmin, orosomucoid, and alpha-2 macroglobulin. Further isolation is being attempted at the present time.

In conclusion, an alpha-2 hyperglobulinemia has been observed in the serum of patients undergoing renal graft rejection. Its persistence in our patients tendered an unfavorable prognosis for the graft while its absence indicated the unlikelihood of the homograft reaction.

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A New Approach to Transvenous Bedside Pacing

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Emergency endocardial pacing under direct vision requires transportation of an acutely ill patient to radiographic facilities and delays therapy. To obviate these difficulties a new technique of transvenous endocardial pacing performed at the bedside was developed that uses a new Elecath "semi-floating" unipolar electrode passed through a number 14 Bardic angiocath from a subclavian vein under electrocardiographic monitoring. An indifferent electrode on the chest completed the circuit to the pacemaker.

Ninety-three approaches were made in 79 patients. Fifty-five patients had high degrees of heart block, 21 with an acute myocardial infarction and 4 with digitalis toxicity. Nine patients had failure of a previously implanted pacemaker; 15 had various indications for pacing including bradycardia and hyperkalemia. Bedside pacing was achieved in 66 of the 93 attempts in less than 45 minutes with an average of 17 minutes from the start of the subclavian puncture. Eleven more of the 93 required fluoroscopic aid for final positioning. The duration of pacing was less than 24 hours in 14 patients, 1 to 3 days in 11, and greater than 3 days in 52. Stable pacing in the fixed rate or demand mode was achieved in 85%. The remainder required minor repositioning at the bedside, usually within the first 24 hours. A small pneumothorax produced in two patients from the subclavian vein puncture comprised the only significant complication. No infections, vessel or cardiac perforation by the catheter, or emboli occurred. Induced arrhythmias were limited to a rare premature ventricular contraction that occurred during positioning. This method appears to be a relatively safe, rapid, and simple means of emergency endocardial pacing and in our hands yielded faster, more certain, and more stable results than the approach from the basilic vein using a Davis and Geck electrode. *(Supported in part by U.S.P.H.S. Grant HE 04666-09.)*

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Studies of Serum Cholesterol and Triglyceride in 1,859 Subjects: An Epidemiological and Pathogenetic Interpretation

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Epidemiologic studies linking the serum cholesterol levels of population groups with the incidence of coronary heart disease has stimulated much interest in defining normal or desirable ranges of serum cholesterol.

The purposes of this study were: 1) to document the serum cholesterol and triglyceride levels in the same individual under identical temporal conditions, 2) to study the effects of age and current weight status on the levels of serum cholesterol and tri-

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glyceride, and 3) to compare the relative merits of the serum cholesterol and triglyceride levels as correlates of coronary heart disease.

Serum cholesterol and triglyceride levels were determined in 872 male and 987 female, normal, urban office workers. Both lipids showed a rapid rate of increase in group aged 19 through 40 for both sexes. The mean levels of serum triglyceride for the male decreased above the age of 50, while the mean levels of the female continued at a rapid rate of increase; the serum cholesterol levels of the female behaved similarly. The mean levels of serum cholesterol for the male above the age of 50 attained a plateau at approximately 250 mg.%.

Obese subjects demonstrated higher mean levels of serum triglyceride than persons of normal weight.

The mean level of serum triglyceride and the combined mean levels of cholesterol-triglyceride for the male was found to be statistically significantly higher in the coronary heart disease group compared to noncoronary subjects. This correlation was not found for serum cholesterol.

The rapid rates of increase in serum cholesterol and triglyceride by age were interpreted in the light of their possible pathogenetic influence on coronary heart diseases. *(Supported by The Eighty Maiden Lane Foundation, New York, N. Y.)*

Immunological Protection Against Digitalis Toxicity

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Antibodies with specificity for digoxin have been shown to bind digoxin *in vitro*. The purpose of the present study was to determine whether digoxin-specific antibodies can prevent the undesirable effects of digoxin *in vivo*.

The lethal dose of digoxin was determined by administering 10 ml. of a digoxin-saline solution containing 0.1 to 0.5 mg./kg. to 23 rabbits through an ear vein over a 10-minute period. The electrocardiogram was monitored continuously with an oscilloscopic recorder that used needle electrodes in the four extremities.

Rabbits which received less than 0.45 mg./kg. digoxin showed no toxic effect, while all eight rabbits that received over 0.45 mg./kg. developed an arrhythmia within 25 minutes and died within one hour.

Six rabbits were immunized with a digoxin-human serum albumin conjugate in complete Freund's adjuvant and developed a significant antibody titer to that antigen. These rabbits were given 0.5 mg./kg. digoxin and all lived, in contrast to the nonimmunized rabbits, and with continuous monitoring all except one showed no significant change in heart rate or rhythm.

To determine whether this was a specific protection provided by antibodies to the digoxin component of the conjugate and did not reflect nonspecific immunological response to a hapten-albumin conjugate, two rabbits were immunized with a folic acid serum-albumin conjugate. When given 0/5 mg./kg. digoxin, both showed signs of toxicity and died as did the nonimmunized rabbits.

This study indicates that rabbits protected by digoxin-specific antibodies suffered no acute adverse effects from an amount of digoxin which is uniformly lethal in nonimmunized rabbits. This protection is specific since animals whose sera contained antibodies to serum albumin and another hapten were not protected. The use of digoxin-specific antibodies in the treatment of experimental digitalis toxicity is currently being investigated. *(Supported in part by U.S.P.H.S. grants HE-05741-07, HE-02001-13, HE-10608-02, and AM-07183-05.)*

Effects of Diphenylhydantoin on Membrane Potentials of Purkinje and Ventricular Muscle Fibers in Dog Heart

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Effects of 10^{-8} to $10^{-4}M$ diphenylhydantoin (DPH) were studied on electrically driven and spontaneously beating isolated, perfused, false tendon-papillary muscle preparations. In all concentrations, the action potential configuration in the Purkinje fiber showed a greater degree of change than that noted in the ventricular fiber; the most consistent change was a shortening of the repolarization time course. In concentrations of 10^{-8} to $10^{-6}M$ the shortening of repolarization in the Purkinje fiber was primarily due to an increase in slope of the plateau phase (phase 2). At concentrations greater than $10^{-6}M$, the terminal phase of repolarization (phase 3) was also shortened; this caused the inflection between phases 2 and 3 to become indistinct. There was little change in the other phases of the Purkinje action potential. In contrast, the action potential of the ventricular fiber showed only minimal shortening of the repolarization time course, which was observed at concentrations of 10^{-5} and $10^{-4}M$. In spontaneously beating preparations DPH caused a decrease in the action potential frequency, and in 2 of 9 instances administration of $1.2 \times 10^{-4}M$ DPH produced a cessation of electrical activity in both fibers 14 and 21 minutes after respectively. However, resting potential was well maintained in both. When an external electrical stimulus was applied both fibers responded with action potentials of normal magnitude, indicating that the cells were still excitable. DPH also increased the functional refractory period in both fibers by lowering the threshold for stimulation.

The greater sensitivity of the Purkinje fiber to the action of DPH compared to the ventricular fiber may explain the effectiveness of DPH in abolishing ventricular arrhythmias. Diphenylhydantoin may abolish the ectopic focus in the Purkinje fiber by increasing its functional refractory period or by decreasing the automaticity by lowering the slope of diastolic depolarization. In this respect its mode of action resembles quinidinelike drugs which lengthen the repolarization time course whereas DPH shortens it. *(Supported by U.S.P.H.S. Grant HE 09337.)*

Protein and Nucleic Acid Incorporation Studies in Perfused Normal and Hypertrophied Rat Hearts

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Isolated nonfasted male rat hearts were perfused with tritiated leucine or lysine in Krebs-Ringer bicarbonate solution via Langendorff retroperfusion of the coronary bed. After varying perfusion periods, the hearts were homogenized. Label incorporation into aa-tRNA (4S peak radioactivity following sucrose gradient centrifugation of phenol-extracted RNA) and into protein (hot TCA precipitate) was measured. Transfer RNA binding of the amino acid label was complete within 5 minutes, and the aa-tRNA pool turnover was likewise rapid; the label was "chased" by unlabeled amino acid within 5 minutes. There was a simultaneous increase in protein-incorporated counts. Pilot studies demonstrate a reduced aa-tRNA pool in experimental ischemic hypertrophy. When nucleic acid precursors were perfused, 90 to 95% of the label entered KOH-soluble RNA, while the remainder was incorporated into KOH-insoluble DNA. ^{3}H guanosine incorporation was 10% in 5 minutes and maximal within 30 minutes. Acute hypoxia ($pO_2 < 50$ mm. Hg) doubled ^{3}H guanosine incorporation into cold TCA precipitate. In monocrotaline-induced RVH, there was a marked increase in the incorporation of ^{3}H guanosine into cold TCA precipitate. Descending rates of nucleic acid precursor incorporation were observed for ^{3}H adenine, ^{3}H guanosine, and ^{3}H guanine. The incorporation of ^{3}H adenine was readily exchangable by cold chase. *(Supported by a grant from the New York Heart Association.)*

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Correlations of Coronary Angiography with Metabolic and Electrocardiographic Studies

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Obstructive coronary artery disease may result in electrocardiographic and myocardial metabolic abnormalities at rest and following catecholamine induced stress. Selective coronary angiography was performed on 40 patients with angina pectoris or previous myocardial infarction. Aerobic myocardial metabolism was evaluated at rest, following isoproterenol infusion, and sublingual administration of nitroglycerine. Arterial-coronary sinus lactate differences were used as a measure of aerobic metabolism (>10% lactate utilization is normal).

Resting EKG's were abnormal in 30 of 40 (75%) patients, with 21 indicative of

infarction. Postexercise traces were abnormal in 2 of 9 (total abnormal EKG's 82%). Thirty-five (87%) patients had severe (>75% obstruction) double or triple vessel disease, 3 (8%) severe single vessel disease, while 2 (5%) had normal angiograms with abnormal EKG's and anaerobic metabolism.

Metabolic studies in 32 cases revealed anaerobic metabolism at rest in 8 (25%), and in 14 additional patients (44%) with stress (total 70%). Of these 2 (6%) had resting angina, and 8 (25%) developed angina during isoproterenol infusion (2-6 γ/min.). Neither patient with resting angina had relief from nitroglycerine (gr. 1/150 sublingually), while 3 of 8 with stress angina did. No patient had restoration of aerobic metabolism within 3 minutes of nitroglycerine administration.

These studies indicate that anaerobic metabolism may occur at rest or be induced with catecholamine stress in a large percentage of patients with severe obstructive coronary artery disease and may not be accompanied by angina pectoris. Although pain may be relieved by nitroglycerine, lactate production may continue. This finding suggests that lactate is not pain inciting, and that pain may be relieved without reversal of ischemia. *(Supported by U.S.P.H.S. Grant 5-T02-HE-00303-19.)*

The Direct Chronotropic Action of Digitalis

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We have tested the widely accepted hypothesis that digitalis exerts a direct negative chronotropic action on the sinus pacemaker of the heart and that this action contributes to digitalis-induced sinus bradycardia. All neural influences on the heart rate of rabbits, cats, and dogs were eliminated by use of appropriate autonomic blocking agents, surgical denervation, or a combination of these methods. After blockade with atropine and either propanolol or MJ-1999, ouabain, and acetylstrophanthidin in doses up to and including those necessary to cause glycoside-induced ventricular tachycardia, did not slow the sinus rate in animals which, under control conditions, did respond to comparable doses of glycoside by a 25 to 40% reduction in the sinus rate. Because of the possibility that an action of the autonomic blocking agents employed might mask a direct negative chronotropic action of digitalis, similar experiments were made on dogs in which the heart had been chronically sympathectomized and acutely vagotomized. These dogs received no drugs other than an anesthetic (chloralose, 40 mg./kg. and urethrane, 400 mg./kg.) and the cardiac glycoside employed (ouabain, up to 0.05 mg./kg. or acetylstrophanthidin, up to 0.075 mg./kg.). Prior to denervation, these animals responded to cardiac glycoside by a slowing of sinus rate; after their hearts had been denervated, similar doses of cardiac glycosides no longer had any negative chronotropic effect. In fact, a slight sinus acceleration was noted just prior to the onset of digitalis-induced ventricular tachycardia. These results were obtained without exception from 60 experiments on 25 animals. They indicate that there is no direct effect of digitalis on the sinus pacemaker which contributes to digitalis-induced sinus bradycardia and that the sinus bradycardia caused by digitalis in normal control animals results entirely from interactions between the glycoside and the autonomic nervous system. *(Supported by U.S.P.H.S. Training Grant 5T01-GM00438 and Research Grant 5R01-HE08508.)*